REMARKS

Claims 43-48, 50-57 and 61-66 will remain pending in the present application upon entry of this amendment. Claims 43 to 45 have been amended..

The Applicant respectfully submits that no new matter is introduced into the application by way of the instant claim amendments. Support for the subject matter of the amendment 'a RNA nucleotide sequence corresponding to' can be found throughout the application as filed on e.g. on page 7, lines 24 to 43 of international applications as filed, wherein it is said that the sequences SEQ ID NOs 13 and 15-17 is transcribed from the + strand of SEQ ID NO 1 and SEQ ID NO 5 (the genomic clones) clearly indicating that the detected sequences in the disclosed assays are RNA transcripts that are transcribed from the recited cDNA sequences..

Claim Rejections - 37 CFR 1.75

Claims 50 have been rejected under 37 CFR 1.75 as being improper dependent form for failing to further limit the subject matter of the previous claim. This rejection is respectfully traversed.

Contrary to the Office Action it is submitted that this is a proper dependent claim that limits the scope of the claims from which it depends. At the outset it should be noted that SEQ ID NO 13 represent Exon 1, not represent Exon 3 (SEQ ID NO 16 corresponds to Exon 3). Moreover, alignment of the sequence contained in SEQ ID NO 13 to all the sequences in claim 50 reveals that SEQ ID NO 13 (Exon 1) is present all of the sequences SEQ NO 11, SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 10. Therefore the detection of all of these sequences recited in claim 50 is correct as it is a subgenus of the sequences recited in the independent claims from which it depends.

Applicant respectfully submits that claim 50 limits the scope of the claim to the specific transcripts listed in the claim (SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 10 and SEQ ID NO: 10). In claims 43, 44 and 45 the at least one transcriptional product is elected from a longer list further including a transcriptional product comprising a the complementary RNA sequence selected from the list consisting of to the complementary RNA sequence to SEQ ID No: 13, the complementary RNA sequence to SEQ ID No: 15, the

complementary RNA sequence to SEQ ID No: 16, and the complementary RNA sequence to SEQ ID No: 17.

Therefore, based on the foregoing withdrawal of the objection to claim 50 is respectfully submitted.

Claim Rejections - 35 USC § 112

Claims 43-48, 50-57 and 61-66 have been rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement.

The Examiner considers that the specification does not disclose detection of DNA in diagnosing B-CLL and further that the specification does not disclose detection of RNA transcripts comprising only SEQ ID NOs 13 or 15-17. The position of the Examiner is respectfully traversed to the extent it may be applicable to the claims as amended. In this regard the claims are amended without prejudice to recite assay methods for detecting one or more sequences that correlate to a specific subtype of CLL wherein all of the detected sequences are RNA transcripts.

Traversal of Rejection Basis Regarding alleged detection of DNA in diagnosing B-CLL

As noted above the claims have been revised to make clear that the detected sequences corresponding to the sequences in SEQ ID NOs 13 and 15-17 are the corresponding RNA transcripts and therefore the claims do not claim detection of DNA sequences. Particularly, the recited sequences all align perfectly to the sequence of the primary transcript (SEQ ID No: 11). The Examiner has acknowledged this fact at page 2, paragraph 4, lines 2 to 5 of the present Office Action.

Therefore it is clear from the wording of the current claims that Applicants in the subject assays are detecting an RNA molecule corresponding to the cDNA sequences contained in SEQ ID NOs 13 and 15-17. Based thereon the subject assay methods do not detect DNA sequences but rather detect for one or more RNA transcripts which in turn are sub-sequences or fragments of SEQ ID No: 11..

Pin this regards it is clear from the revised claim wording (which is consistent with he express teachings of the application) that the pending claims concerns detection of at least one transcriptional product, wherein said at least one transcriptional product comprises a RNA

sequence from the group consisting of SEQ ID No: 2, SEQ ID No: 4, SEQ ID No: 6, SEQ ID No: 7, SEQ ID No: 10, SEQ ID No: 11, or is an RNA transcript which corresponds to the cDNA in any of SEQ ID No: 13, SEQ ID No: 15, SEQ ID No: 16, and SEQ ID No: 17 in a biological sample isolated from the individual.

It is clear from the wording of the claim, using the term transcriptional product, and the recitation of detected RNA sequences that the subject matter of the claims is not directed to the detection of genomic DNA in diagnosing B-CLL. The specification clearly teaches that the subject matter of the invention concerns detection of at least one transcriptional product., i.e., in the present instance specific RNA transcripts.

In this regard t is clear from the specification that whereas the sequences that the SEQ ID NOs 13 and 15-17 are cDNA (corresponding DNA) sequences that the disclosed assays in fact detect the RNA transcripts corresponding to the cDNA sequences as these transcripts are only expressed in subjects with the subject virulent subtype of CLL. The skilled person would readily understand from the teachings of the application that the subject matter of the claims concerns detecting at least one transcriptional product comprising a RNA nucleotide sequence which is selected from the RNA sequences contained in any of SEQ ID No: 2, SEQ ID No: 4, SEQ ID No: 6, SEQ ID No: 7, SEQ ID No: 10, or SEQ ID No: 11, or the detected RNA transcript is a transcribed sequence (corresponding to of any of the cDNA sequences) set forth in SEQ ID No: 13, SEQ ID No: 15, SEQ ID No: 16, or SEQ ID No: 17.

It would be apparent from the specification the term transcribed sequence of the recited cDNA sequences derives from the finding that RNA (such as RNA) can be reverse transcribed into DNA by reverse transcriptase. The product of the reverse transcription is the referred to as a transcribed sequence which corresponds to a particular complementary DNA (cDNA). Accordingly, while a particular cDNA and the corresponding RNA sequence are technically different chemical entities the terms are often used interchangeably by those person skilled in the art to uniquely define the primary structure of a RNA transcript in question.

The fact that cDNA sequences and RNA sequences are used interchangeably to describe the primary structure of RNA such as a transcript is evident from looking up a random sequence entry relating to a transcript on NCBI.

For example, a search string including the terms 'p53' and 'transcript' identifies NM_001166390.1. The title of the entry 'the Mus musculus protein tyrosine phosphatase 4a3 (Ptp4a3), transcript variant 4, mRNA' (emphasis added) clearly indicates that the sequence in question is the mRNA sequence. However, the sequence is displayed as a DNA sequence, the complementary DNA sequence to the transcripts. The above also applies to other randomly picked entries such as NM_021783.2, NM_001166241.1, and NM_001145339 identified by the same search.

In fact, none of the randomly picked sequence displayed the sequence in the form of an RNA sequence although the title indicated that the matter concerned mRNA. All inspected entries displayed the RNA sequence in the form of a DNA sequence (the complementary DNA sequence to the transcript). The Applicant respectfully submits that any ordinary skilled person would acknowledge that reference RNA sequence and the corresponding DNA sequence may be used interchangeably in the context of the claimed invention and more impoartantly that Applicants' specification provides assays for detection of one or more transcribed sequences as set forth in the present claims..

Particularly, in order to expedite the prosecution of the present application the Applicants have revised the wording of the claims to make even more explicit that the sequences listed in the claims are RNA transcripts and that the claimed assays are directed to detecting at least one transcription product, wherein said at least one transcription product comprises a RNA nucleotide sequence selected from the group consisting of SEQ ID No: 2, SEQ ID No: 4, SEQ ID No: 6, SEQ ID No: 7, SEQ ID No: 10, SEQ ID No: 11, or is a transcribed RNA sequence corresponding to any of the cDNA sequences recited in SEQ ID No: 13, SEQ ID No: 15, SEQ ID No: 16, and SEQ ID No: 17 in a biological sample isolated from the individual.

Traversal of Rejection Basis alleging non-enablement of assays that detect RNA transcripts comprising SEQ ID NOs 13 and 15-17.

The Applicant respectfully disagrees and traverses the rejection of the claims as allegedly failing to comply with the enablement requirement. It is assumed that this rejection was made because of the alleged ambiguity of the claimed assays i.e., that they were in some aspects apparently directed to detection of cDNAs rather than RNA transcripts. This should be moot based on the present amendments.

However, for completeness the rejection is further respectfully traversed if indeed the Examiner considers that the specification does not disclose detection of RNA transcripts comprising only SEQ ID NOs 13 and 15-17.

In this regard the Office Action correctly states in the 35 U.S.C. §112, first paragraph section of the Office Action that *the "enablement requirement is satisfied when one skilled in the art, after reading the specification, could practice the claimed invention without undue experimentation." "The fact that some experimentation is necessary does not preclude enablement; what is required is that the amount of experimentation 'must not be unduly extensive."* (AK Steel Corp. v. Sollac & Ugine, 344 F.3d 1234, 1244 (Fed. Cir. 2003); see also In re Wands, 858 F.2d 731, 737, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988), PPG Indus., Inc. v. Guardian Indus., Corp., 75 F.3d 1558, 1564, U.S.P.Q.2d 1618, 1623 (Fed. Cir. 1996) (quoting Atlas Powder Co. v. E.I. DuPont de Nemours & Co., 750 F.2d 1569, 1576 (Fed. Cir. 1984)).

This is not disputed. In fact one skilled in the art could practice the full scope of the claims absent undue experimentation. The Applicant notes that the amended claims concern detecting the presence or absence of at least one transcription product, wherein said at least one transcription product comprises a RNA nucleotide sequence selected from the group consisting of SEQ ID No: 2, SEQ ID No: 4, SEQ ID No: 6, SEQ ID No: 7, SEQ ID No: 10, SEQ ID No: 11, or is a transcribed RNA sequence (corresponding to any of the cDNA sequences) set forth in any one of SEQ ID No: 13, SEQ ID No: 15, SEQ ID No: 16, and SEQ ID No: 17 in a biological sample isolated from the individual.

The present application clearly teaches detecting the presence or absence of transcript(s) of CLLU-1 – thus transcript(s) comprising a RNA nucleotide sequence selected from the group consisting of SEQ ID No: 2, SEQ ID No: 4, SEQ ID No: 6, SEQ ID No: 7, SEQ ID No: 10, SEQ ID No: 11, or a transcribed RNA sequence (corresponding to any of the cDNA sequences) set forth in any one of SEQ ID No: 13, the complementary RNA sequence to SEQ ID No: 15, the complementary RNA sequence to SEQ ID No: 16, and the complementary RNA sequence to SEQ ID No: 17 in a biological sample isolated from the individual.

The application as filed discloses the detection of several species falling within the claims by means PCR or hybridization.

For example the Northern blot in Figure 3 detects at least three species comprising SEQ ID No: 16. The supplementary data submitted with the previous response, detects at least three species comprising SEQ ID No: 13.

It is well known in the art, that the signal corresponding to a species of transcripts on a Northern blot the strength depends on several factors including the abundance of the transcript in the sample, size of transcripts, and time of exposure of the radiogram. In order to detect rare transcripts long exposure is needed. It falls within the capabilities of the skilled person to consider longer exposures if he prefers to detect rare transcript. The Applicant respectfully draws Examiner attention to Northern blot in Figure 3, which shows that the primary transcripts (and two abundant transcripts) are only present in the unmutated subtype. Thus, the detection of at least one transcription product, wherein said at least one transcription product comprises a RNA nucleotide sequence selected from the group consisting of SEQ ID No: 2, SEQ ID No: 4, SEQ ID No: 6, SEQ ID No: 7, SEQ ID No: 10, SEQ ID No: 11, the complementary RNA sequence to SEQ ID No: 13, the complementary RNA sequence to SEQ ID No: 15, the complementary RNA sequence to SEQ ID No: 16, and the complementary RNA sequence to SEQ ID No: 17 is shown to be operative and enabled based on the explicit teachings of the application.

Further, the application includes data detecting at least one transcription product comprising the two Exon sequences by means of PCR using primers flanking the Exon-Exon junctions.

The Applicant respectfully submits that the application meets the enabling requirement because the Example disclosed is representative for the established diagnostic/prognostic utility of the claimed method. If he desires, the ordinary skilled person would known how to apply a wide range of means of detection to identify other species of transcription product comprising a RNA nucleotide sequence selected from the group consisting of SEQ ID No: 2, SEQ ID No: 4, SEQ ID No: 6, SEQ ID No: 7, SEQ ID No: 10, SEQ ID No: 11, the complementary RNA sequence to SEQ ID No: 13, the complementary RNA sequence to SEQ ID No: 15, the complementary RNA sequence to SEQ ID No: 16, and the complementary RNA sequence to SEQ ID No: 17.

The specification of the international application as filed page 2, lines 25 to 27 teaches that the "presence of an expression product of the AMB-1 gene can be determined easily using standard laboratory procedures and equipment".

The specification page 10, lines 24 to 27 further teaches the presence or absence of the transcriptional product having a sequence corresponding to SEQ ID NO: 2, 4, 6, 7, 8, 9, 10, 11, or fragments thereof can be done by selecting primer pairs which cause only amplification of these sequences.

It is within knowledge of the ordinary skilled person to design the assay to detect rare species transcripts. However, in the clinical application he most likely prefers to establish the assay on an abundant transcript to ensure robustness.

In sum, the Applicant respectfully submits that the skilled person would read the specification of the present application and acknowledge the that presence of transcripts comprising a RNA nucleotide sequence selected from the group consisting of SEQ ID No: 2, SEQ ID No: 4, SEQ ID No: 6, SEQ ID No: 7, SEQ ID No: 10, SEQ ID No: 11, the complementary RNA sequence to SEQ ID No: 13, the complementary RNA sequence to SEQ ID No: 15, the complementary RNA sequence to SEQ ID No: 16, and the complementary RNA sequence to SEQ ID No: 17, correlates with a specific subtype of B-CLL and may be detected absent undue experimentation. The fact that expression of the primary transcript correlates with this subtype would be sufficient for the skilled person to reasonably conclude that this correlation is also present for transcript derived from the primary transcript. The specification discloses the detection of several species falling within the claim by means PCR and hybridization.

The purpose of the [enablement] requirement that the specification describe the invention in such terms that the one skilled in the art can make and use the claimed invention is to ensure that the invention is communicated to the interested public in a meaningful way (MPEP paragraph 2164).

The Applicant submit that the claimed the invention is communicated to the interested public in a meaningful way by disclosing the detection of at least one transcription product comprising at least one of the transcribed sequences (corresponding to any of the cDNA sequences) contained in SEQ ID NOs 13 or 15-17 by means of PCR or Northern blotting. The guidance in the specification regarding the correlation between presence of CLLU1 and the

specific subtype of B-CLL is more than adequately shown , and the specific methods which are utilized to practice the invention (PCR and Northern blotting) were very well known in the art at time the application were filed.

Conclusive remarks

Accordingly, Applicants submit that the scope of claims in the instant application is commensurate with the scope of the enabling disclosure. In light of the instant amendments and remarks provided herein, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 43-48, 50-57 and 61-66 under 35 U.S.C. § 112, 1st paragraph as allegedly failing to comply with the enablement requirement.

Based on the foregoing amendments and remarks it is anticipated that the present amendments will place this case in condition for allowance. A Notice to that effect is respectfully solicited. However, if any issues remain outstanding the Examiner is requested to contact the undersigned.

The Commissioner is hereby authorized to charge payment of any additional filing fees required under 37 C.F.R. § 1.16 and § 1.17 associated with this communication or credit any overpayment to the deposit account of Hunton & Williams, **Deposit Account Number 50-0206.**

Respectfully submitted,

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Dated: October 5, 2009 By: _____

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